

Gray scale assessment of axillary lymph nodes in women suspected of breast cancer.

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Abstract

Purpose of Study

Breast cancer is currently listed as the number two disease in the United States contributing to death in elderly women. Because breast cancer is more prevalent and presents at an advanced stage in older women, less invasive procedures are needed to assess the extent of the disease. Axillary lymph nodes play a major role for staging breast cancer. Ultrasound has the potential to provide noninvasive, non-ionizing, measurements to assess axillary lymph nodes to determine the prognosis of the disease.

Research Method

Fifty four women ages 55 and older were consented for this study. These participants were recruited once they were referred to breast ultrasound following their mammogram. Additional time was allotted for the collection of possibly three axillary lymph nodes, in which the location, size, and shape was recorded. After about 3 months of the patient's breast ultrasound, a chart audit was conducted to obtain pathological reports. These recorded measurements were then compared with published values of other research studies.

Findings

A total of 139 axillary lymph nodes were imaged and evaluated. A strong association was found between the shape of the node and the length to diameter ratio (L/D). This comparison between measures had a calculated statistic p-value < 0.000 . There was also a strong correlation between the L/D ratio and the morphology of the axillary lymph node which had a statistical p-value < 0.024 .

Implications

This feasible study was designed to explore a potential clinical guideline based on the use of L/D ratio and gray scale morphology to assess the axillary lymph nodes. With continued and expanded research, this technique may be used to screen for possible breast cancer metastases among older women at high risk for breast cancer.

Chapter 1

a. Problem Statement:

Breast cancer is currently listed as the number two disease in the United States leading to death in elderly women [1]. Primary breast tumors in elderly women seem to be less aggressive but are in an advanced stage of breast cancer due to the delay of diagnosis, therefore need more aggressive intervention [2]. Because breast cancer is more prevalent in older women, less invasive procedures are needed to assess the progress of breast cancer. In Randolph and Goodwin's recent study found that in a population of 12,000 older women (>75 years of age) the primary tumors were larger and more advanced than cancers detected in women between the ages of 64-74 [3].

Axillary lymph nodes play a major role for staging breast cancer. The lymphatic fluid flows from interstitial spaces between the cells where it carries bacteria and debris. (4) Blind capillaries found within tissue banks take up the lymphatic fluid and funnels it towards a collector vessel which allows no backflow [4]. The lymphatic fluid is then propelled from the collector vessel to the afferent vessels of the lymph node. This fluid travels throughout the node and then exits through the efferent vessels of the hilum where it travels to the next node.

There are three levels in which axillary nodes are divided. Low axillary nodes (Level I) are located lateral to the pectoralis minor muscle. Level II or mid axillary lymph nodes are directly behind or deep to the pectoralis minor muscle. High axillary lymph nodes, also known as level III or subclavian nodes are medial superior to the pectoralis minor muscle [5].

Angiogenesis is a complex process in which new blood cells are formed by pre-existing vascular tissues. When breast cancer is present, debris from the host tumor breaks away and is then carried as debris in lymphatic fluid. The debris (tumor particles) contains proteins which are trapped in the blind capillaries and are transported to the axillary lymph nodes [6].

This process demonstrates how important it is to assess axillary lymph nodes and how they can determine the prognosis of breast cancer. Currently mammography, MRI and sonography are the imaging modalities used to screen patients for breast cancer. A more popular method of determining prognosis of breast cancer is sentinel lymph node dissection (SNLD). This requires a dissection of 6 nodes in order to provide a histological examination. Because of this requirement SNLD is considered the gold standard for regional metastasis [7]. However a less invasive procedure is needed in order to evaluate these axillary lymph nodes. Ultrasound provides noninvasive, radiation free, measurements to assess axillary lymph nodes to determine the prognosis of the disease.

Background:

Using ultrasound to assess axillary lymph nodes provides multiple measurements in order to determine the prognosis of breast cancer and to scan women for possible metastases. For my purposes I will only concentrate on the size and shape of axillary lymph nodes.

The sonographic appearance of a normal axillary lymph node resembles the shape of the kidneys. Although the lymph nodes are much smaller they are both elliptical in shape and contain a cortex and a mediastinum. They appear flat and C-shaped in the

short axis. The opening of the C is where the hilum of the node is located. The size of normal lymph nodes varies depending on the cortex and mediastinum. In general a larger lymph node will result in a fattier mediastinum and a thinner stretched cortex. With repeated inflammation, scarring, atrophy, and weight gain, which occurs with increased age, often causes a fattier mediastinum and thinner cortex. Thus this infiltration of fat causes an increase in the size of the lymph node over time. Because of this, the size alone of axillary lymph nodes is not a perfect indicator of the status of lymph nodes. When there is an infiltration of fat or inflammation and cortical thinning, nodes are often still elliptical in shape. Abnormal lymph nodes tend to become more rounded due to the neoplastic involvement enlarging the short plane of the node. Therefore looking at both the size and shape of the lymph node becomes important in order for proper assessment [5]. It is important to calculate the Length/Diameter (LD) ratio because this can help determine a numerical value that will be affected due to the roundness of the lymph node. According to Lernevall, an LD ratio of <1.5 indicates the node is malignant and a ratio >2.0 indicates the lymph node is more likely to be benign [8].

b. Review of Literature:

Other researchers have assessed axillary lymph nodes using gray scale sonography to measure the size and shape of the nodes. In the research conducted, each researcher used a transducer with a frequency of 7.5 MHz or higher which is the accepted practice to assess disease within lymph nodes [8]. Because of the changes in technologies and equipment, I am limiting my related research to the previous 15 years.

A study in 1998 was conducted of 2 groups of women. The first group consisted of 81 women who had breast cancer and underwent axillary nodal dissection. They were

previously examined using gray scale sonography and color doppler ultrasound. The second group consisted of 106 women who were screened for breast cancer but had no axillary pathology [9]. Although this article concentrates on the results due to color doppler they did assess each patient using gray scale sonography. However, this study was mainly descriptive by only classifying normal nodes as having a fatty central hilum and abnormal nodes showed a loss of fatty hilum. Because it was descriptive it is hard to develop a standard measurement or benchmark value to assess the size and shape of axillary lymph nodes. This study also failed to state the ages of the women in the study. Because breast cancer increases in older women, age is an important factor. It is also important for the study to be age specific because of the changes that occur in axillary lymph nodes over a period of years.

In 2000 another study was performed which consisted of 71 patients ages ranging from 12-83 years. There were 31 males and 40 females who participated in the study. The shape was evaluated along with a measurement of the long to short (L/S) axis ratio. Nodes were scanned in 2 planes, measuring the length (long axis) and the diameter (shortest axis). Again, a value of 2 was classified as the cutoff mark for the lymph nodes being benign [10]. This study also utilized ages ranging from 12 to 83 years. The shape and size were hard to evaluate due to the range of ages. This study also included both males and females, but breast cancer is more prevalent in females. Therefore assessing male lymph nodes did not add to the study results.

Again, another study consisting of 135 women were evaluated using gray scale sonography. One hundred forty five nodes were examined which were divided into palpable nodes and non palpable nodes. The purpose of this study was to determine a

predictive value of gray scale features of axillary lymph nodes for the diagnosis of patient with primary breast cancer. The ages ranged from 28 to 82 years of age. Fine needle aspiration biopsy, lymph node dissection, and cytologic analysis were performed in order to determine malignancies. As a result there was a significant difference in L/W ratios of malignant and benign nodes. The mean L/W axis ratio was significantly lower in malignant nodes compared to benign nodes [11]. However, the ages ranged over a 50 year span.

Another study again concentrated mostly on color doppler but previously used gray scale analysis [12]. There were 114 patients in which neither the gender nor age was recorded. Gray scale was used for the evaluation of the cortex and hilum of the axillary lymph nodes. However this study not only failed to report the age and gender of the patients but was also not axilla specific.

A study in 2003 conducted by Bedrosian gathered patients (205) from their institution's database, who underwent SLN biopsies and had negative axillary nodes [13]. This study's participants ranged from the ages of 26 to 91, and was mainly descriptive in referring to the gray scale assessment of axillary nodes. One criteria for a positive mediastinum was described as the node having a round shape.

A study designed to compare the usefulness of gray scale and color doppler sonography was performed within 59 participant's ages 14 to 78 years old. Gray scale had a sensitivity of 92%, a specificity of 70%, and an overall accuracy of 85%. When combined with color doppler the sensitivity and overall accuracy increased but the specificity remained the same [14]. Again the ages ranged over a 60 year age span.

A more recent study retrospectively looked at 30 patients ranging from ages 30 to 65 years. They used sonographic images to evaluate the size of the lymph node, an absence of a fatty hilum, abnormal cortex and the round versus oval shape of the lymph node [15]. The study was more age specific but it still should be more selective to women ages of at least 50 years and older or postmenopausal. I do like how they used multiple gray scale techniques to evaluate the size, shape and morphology of the lymph nodes.

The study conducted in 2005 by Esen has been the most rigorous compared to the other previous studies. Eighty five women ages ranging from 30 to 78 each were examined using gray scale and color doppler ultrasound. There was a maximum of 3 nodes evaluated per patient if found in the allotted time frame of 15 min. Two hundred and three lymph nodes were evaluated. The images were digitally recorded and the location of the lymph nodes along with a 2 dimension axis was also recorded. One experienced radiologist performed all examinations. Once the dimensions were recorded a L/D ratio was calculated. Each node was then evaluated for and absence of hilum, cortical thickening, and asymmetric cortical thickening [16]. This study provides a more reliable set of information and a specific benchmark could be developed from their gray scale analysis. Because it was performed by only one radiologist and because there were a large number of lymph nodes which were evaluated produces more reliable, consistent findings. The location and exact measurement is also important for evaluating the lymph nodes. The only drawback of this study is the age population. This study should be a little more age specific to truly represent the high risk of breast cancer.

Although many research projects have addressed similar areas, not one study has been age specific for gray scale analysis of axillary lymph nodes. Because lymph nodes change with the incidence of age and breast cancer is so specific to women in the upper 50's, it is critically important to try to represent this population to the best of our ability to produce reliable information.

c. Objective:

The objective of this study was a preliminary data collection to determine a benchmark value of the L/D ratio by assessing axillary lymph nodes, using gray scale sonography. The sonographic assessment of the axillary lymph nodes could potentially screen breast cancer metastases in older women by using non invasive measurements.

Hypothesis:

An L/D ratio benchmark for axillary lymph nodes would help assess and screen patients for breast cancer combined with other measurements of sonography.

If sonographic assessment is valuable in determining the prognosis of breast cancer, then ultrasound is a feasible examination that can be put into clinical practice with the proper training and practice.

Research Questions:

- Is there an L/D ratio benchmark that determines if the lymph node is benign or malignant?
- Does the size of axillary lymph nodes correspond to breast cancer malignancy? If so, is there a benchmark value that can help determine malignant nodes?
- Does the morphology of a more rounded, sphere-shaped axillary lymph node correspond to the malignancy of axillary lymph nodes?
- Does ultrasound provide reliable, consistent measurements aiming to help diagnose breast cancer patients by using non-invasive measurements?

Chapter 2

a. Methodology

My study is a part of a larger research project. The entire project records and analyzes other sonographic measurements in screening the patient for breast cancer. Color doppler is also being measured for axillary lymph nodes to produce more reliable information. I am independently assessing the gray scale sonographic component of axillary lymph nodes which includes the size, shape, morphology and the calculated L/D ratio. My part of the research project is able to continue without the other parts of the sonographic assessment but is far more reliable and accurate using multiple measurements of axillary lymph nodes.

Internal Review Board (IRB) approval is needed due to the participation of human subjects. A proposal of the study was sent to the IRB explaining the project, participant criteria, possible risks and benefits, confidentiality, data collection methods, recruitment and informed consent. There are two consent forms that need to be signed by both the researcher and the participant. This research project received IRB approval.

b. Population and Sample

The sample population of my research will be obtained at The Ohio State University East Hospital. Women patients who had a mammogram and were referred for a breast ultrasound, ages 55 years and older, will meet the criteria to be a part of my study. Patients who previously had breast cancer surgery will be excluded from my sample. The sample size will be 54 women with a maximum of 3 lymph nodes per affected axilla side.

c. Design:

This research project was designed as a feasible study to determine if ultrasound assessment of axillary lymph nodes was a reliable diagnostic imaging measurement for staging breast cancer. The collection of axillary data was obtained in conjunction with the patient's breast ultrasound which was a follow up examination after the patient's mammogram. Written consent was obtained at the beginning of their breast examination. The patient's participation was completed voluntarily and were able to withdraw from the research at any point. An additional 15 minutes was allotted to obtain the axillary information. This time allowed collection of possibly three axillary lymph nodes, in which the location, size, and shape was recorded. All images were digitally saved which allowed the cases to be accessible if more information needs to be obtained. After about 3 months of the patient's breast ultrasound, a chart audit was conducted to obtain pathological reports. One registered diagnostic medical sonographer (RDMS) performed all breast ultrasound examinations along with the axillary data collection. All data collected was completed at The Ohio State University East Hospital.

d. Data and Instrumentation:

A data collection instrumentation form was used to obtain the recorded data of the participant. The data form included the patient's accession number, along with the date of their previous mammogram and the date of the breast ultrasound examination. The Breast Imaging Reporting and Data System (BI-RADS) code included was determined by the mammogram report. The location of each axillary lymph node was recorded as level I, level II or level III. The length, width and height of each lymph node was measured and recorded on the data form. The node was evaluated and recorded as either round or

oval shaped. The form included information regarding the doppler evaluation of the axillary lymph node, but for my purposes, the focus was on the gray scale analysis.

The design of the research was reliable because the data collection was conducted by only one sonographer. There were a total of 54 participants all over the age of 55 years. This provided 139 nodes evaluated from a sample population that was representative of the breast cancer population of elderly women. This produced consistent measurements of the axillary lymph nodes. The instrument was valid because it measured exact characteristics which were obtained in order to produce diagnostic information of breast cancer. Although the ultrasound analysis of axillary lymph nodes was not the gold standard measurement, it provided diagnostic information as a less invasive measure.

Analysis of the data collected will be done with SPSS. Calculations such as mean/ averages, and L/D ratios will be calculated and compared to analyze the data more efficiently. A data table was created at the conclusion of the research which included the pathological reports of the participants.

Facilities and/or Resources and Equipment Needed:

In order for this research to be conducted, The Ohio State University East Hospital allowed their facility and staff to collect the data. The computer program SPSS was available to organize and statistically calculate the data. Each participant's images of the axillary study were digitally stored and capable of archiving. To reevaluate and examine these images a computer communication system was needed to archive the participant's charts and examinations.

Significance of the proposed work:

This was designed as a feasible study of axillary lymph nodes to determine if ultrasound was a feasible examination in determining the prognosis of breast cancer. This research study was significant because it filled the gap that the other studies failed to provide. A study designed to help diagnose breast cancer patients should target the population most at risk for developing the disease. Because older women are at higher risk of breast cancer, the research study should provide gender and age specific information in order to set accurate and reliable guidelines for sonographic assessment of axillary lymph nodes.

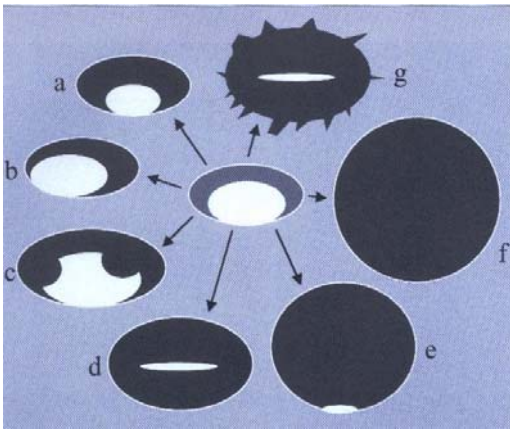
Chapter 3**a. Results**

A total of 54 patients were consented to be a part of the study. However, on two patients no nodes were found in the 15 minute time frame. Of these 52 patients a total of 139 axillary lymph nodes were found and evaluated. Ideally three nodes were to be found and evaluated for each patient. Due to the time available three nodes were not available for every patient. In 39 patients, all 3 nodes were found and examined. In 10 patients two nodes were found and in 3 patients, only one node was found. At the time of the examination, nodal dimension measurements were recorded. The dimension measurement converted to an L/D ratio, which represented the longitudinal length over the diameter of the axillary lymph node. Later after the exam, subjective morphologic assessment were made to the nodes by reviewing the images on PACS. The images were evaluated using Stavros morphologic scale (figure 1). It was also at this time when the shape of the node was evaluated. It was determined as either round or oval. Oval

appearances were identified with being benign nodes compared to a more round shape which represents malignancy. Nodes on every patient were evaluated in this fashion.

Figure 1.

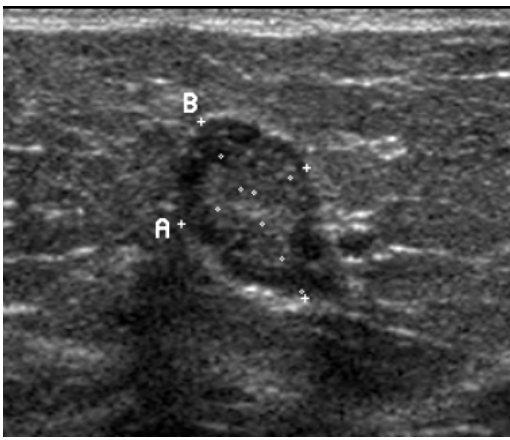
Stavros Range of Abnormal Sonographic LN Appearances [5]



Descriptive statistics for the L/D was expressed. The L/D ratio was compared to a 1.5 L/D published value. A statistically significant p-value < 0.05 was established a priori. The data analysis was performed using Windows SPSS 15.0. The mean L/D ratio was 1.6 (SD 0.48). Of the lymph nodes evaluated, 47% were less than 1.5 and 53% were greater than or equal to 1.5 (Figure 2).

Figure 2.

Longitudinal axis measurement compared to diameter of lymph node (L/D Ratio)



A=0.86, B=1.35, L/D Ratio=1.57

The shape of the lymph node was qualitatively evaluated either as round or oval. Of the nodes evaluated, 14% had a round appearance and 86% were oval shaped. The morphology of the nodes was classified as either normal or possessing metastatic qualities. Using Stavros scale, this includes c,e,f and g (see figure 1). There were 74% of nodes classified as normal and the other 26% possessed metastatic qualities.

L/D Ratio and Shape

Comparisons between measurements were made to explore possible correlations. A strong association was found between the shape of the node and the L/D ratio. Published studies have suggested a ratio of < 1.5 cm on a sonographic image should be considered abnormal [16]. Oval nodes were more likely to have an L/D ratio greater than or equal to 1.5. Out of 139 nodes, 97% of the oval nodes had an L/D ratio greater than or equal to 1.5 in which 2.7% were round nodes. This comparison between measures had a calculated statistic p-value $< .000$.

L/D Ratio and Morphology

The L/D ratio was also compared to the morphology of the node. The 1.5 cm published value was used for this comparison as well. Again, there was a strong statistical correlation between the two measures. Seventy-eight percent of normal morphology nodes (scores 0,a,b&d) had an L/D ratio greater than or equal to 1.5 and 22% of abnormal morphology nodes (scores c,e,f&g) had an L/D ratio < 1.5 . This had a calculated statistical p-value of 0.024.

Pathology

Although this was a feasible study on gathering sonographic data, we did not follow as many patients through their pathologic path. Because of the random nature of scanning three lymph nodes, the pathologic report cannot be directly related to the pathologic characteristics of the lymph nodes. Of the 54 patients consented three women had reported malignant breast cancer. Lymph node pathology reports were also tracked and thus far no patient had malignant lymph pathology.

b. Discussion

Breast Cancer is the number two leading cause of death of women in the United States. Because the risk escalates for women over 50 years, a more efficient screening technique is needed along with less invasive interventions to determine axillary nodal involvement. A great deal of research has been conducted for detection of breast cancer and associated metastasis. Our study concentrated on using sonography to measure the axillary lymph nodes among potential breast cancer patients.

Our study concentrated on imaging the axillary lymph nodes, but was specifically targeted for women 55 years and older. The study was designed as a feasible study in confirming a clinical guideline for using L/D ratio and morphology to assess grayscale sonography of the axillary lymph nodes. This could help screen possible breast cancer metastases among women utilizing this non-invasive technique.

Fifty four patients were recruited as part of our study. However, due to two patients not having lymph nodes imaged during the allotted time, only 52 patient's information was used. If all three nodes were examined in all 54 patients, that would

produce 162 nodes evaluated. However, with 52 patients and a maximum of three lymph nodes per patient, 139 nodes was still sufficient to be found and examined. We only allotted 15 minutes for the axillary exam, it was difficult to find and measure three nodes. For our study we found 139 nodes in these 54 patients, which is still about 86% effective for the first time trying this study. This demonstrated that this sonographic technique is clinically time efficient and could provide useful data with proper training and experience.

In evaluating these nodes, the L/D ratio paired with the shape of the node proved to be correlated with high statistical significance. The L/D ratio when coupled with the morphology of the lymph node also proved to have a strong correlation for assessment with statistical significance. Because of these results, our study has advanced the field in developing a clinical guideline for diagnostic sonography. Our study only consisted of 54 patients and in order to generalize the results, a larger study needs to be conducted.

In our study it was not possible for us to know exactly which lymph nodes were evaluated. Therefore it was not possible to compare their ultimate pathology results to the specific nodes that were imaged. Because of our statistical significance, it may be assumed; however, that a connection exists and further studies are needed with this age group of women.

Our study was designed to see if this would be a feasible imaging method to help screen for breast cancer metastasis among older female patients. It is possible due to the time frame allotted, lymph nodes obtained, and measured to obtain these parameters. In our study only one trained sonographer performed these examinations. In order to conduct a larger study based on the workload, the staff would need to be trained to find

and measure the axillary lymph nodes properly. Although it is challenging at first, with proper training and experience, this may be a valuable tool in conjunction with other exams and modalities in diagnosing metastatic breast cancer.

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